PATENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 August 2000 (22.08.00)	
International application No. PCT/SE99/02197	**Applicant's or agent's file reference** 2006184
International filing date (day/month/year) 25 November 1999 (25.11.99)	**Priority date** (day/month/year) 25 November 1998 (25.11.98)
Applicant ERIKSSON, Peter	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   21 June 2000 (21.06.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Nestor Santesso
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC-2006184	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE99/02197	International filing date *(day/month/year)* 25.11.1999	Priority date *(day/month/year)* 25.11.1998
International Patent Classification (IPC) or national classification and IPC7 A 61 K 38/27, C 12 N 5/06		
Applicant A+ Science Invest AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.06.2000	01.03.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Carolina Palmcrantz/ELY Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/02197

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-14 , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statement) under article 19
pages _____ , filed with the demand
pages 15-18 , filed with the letter of 12.02.2001

☒ the drawings:
pages 1-2 , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☐ the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 14-31

because:

☒ the said international application, or the said claims Nos. 14-31
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

PCT Rule 67.1(iv): Methods for treatment of the human or animal body by therapy.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

As is stated in Annex B to Administrative instructions under the PCT, in force July 1, 1992 (PCT GAZETTE 1992, June 25, pages 7062-9, see page 7063 and example 5) unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features" - i.e. features that define a contribution which each of the inventions makes over the prior art. (c.f. PCT Rule 13.2)

A search for this "special technical feature" mentioned in PCT Rule 13.2 among the independent claims did not reveal such a unifying, novel technical feature. Accordingly, the following inventions were found:

Invention A, claims 1-10 and 13, concerns the use of a substance that upon administration to a patient will lead to an increased concentration of growth hormone for the production of a medicinal product for treatment of a CNS damage affecting neural stem cells, progenitor cells and/or cells derived from stem cells or progenitor cells.

.../...

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. _____

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.

Invention B, claims 11-12 , concerns the use of a substance that upon administration to a patient will lead to a decreased concentration of growth hormone for the production of a medicinal product for treatment of an abnormal condition affecting the central nervous system, wherein said abnormal condition is the consequence of axonal damage caused by concussion, axonal damage caused by head trauma, axonal damage caused by small vessel disease in the CNS, or damage to the spinal cord after disease and/or trauma.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	7,11-13	YES
	Claims	1-6,8-10	NO
Inventive step (IS)	Claims	11-13	YES
	Claims	7	NO
Industrial applicability (IA)	Claims	1-13	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Amended claims 1-31 were filed 12.02.2001. Claim 1 has been restricted in that the abnormal condition is a CNS damage. Claim 11 comprises the determinations of old claim 15, i.e. it has been restricted to abnormal conditions as a consequence of axonal damage caused by concussion, axonal damage caused by head trauma, axonal damage caused by small vessel disease in the CNS, damage to the spinal cord after disease and/or trauma. Claim 13 has been restricted to concern a method for in vitro propagation of progenitor cells, stem cells and cells derived thereof.

Thus, the present application, as defined by claims 1-10 and 13, pertains to the use of a substance that upon administration to a patient will lead to an increased concentration of growth hormone, or a functionally equivalent analogue thereof, for the production of a medicinal product for treatment of a CNS damage affecting neural stem cells, progenitor cells and/or cells derived from stem cells or progenitor cells. Such abnormal condition is for instance caused by hypoxic injury, ischemic injury and/or traumatic injury.

The wording "a substance that upon administration to a patient will lead to an increased concentration of growth hormone or a functionally equivalent analogue thereof" of claim 1 defines the substance in terms of a result to be achieved. The claims cover all substances having this property, whereas the application provides a clear support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such substances, i.e. GH and GHRP. As a consequence, the international search, upon which this statement is based, has been incomplete.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V.

Further, the application, as defined by claims 11-12, concerns the use of a substance that upon administration to a patient will lead to a decreased concentration of growth hormone or a functionally equivalent analogue thereof for the production of a medicinal product for treatment of an abnormal condition affecting the central nervous system (CNS), wherein said abnormal condition is the consequence of axonal damage caused by concussion, axonal damage caused by head trauma,axonal damage caused by small vessel disease in the CNS, or damage to the spinal cord after disease and/or trauma.

The wordings "a substance that upon administration to a patient will lead to a decreased concentration of growth hormone or a functionally equivalent analogue thereof" of claim 13 and "negatively regulating growth hormone binding protein", "a functionally equivalent analogue thereof ", growth hormone receptor inhibitor", and "inhibitor of endogenous growth hormone release" of claim 14 define the intended substances in terms of a result to be achieved. The claims cover all substances having this property, whereas the application do not give any specific examples of substances (c.f. PCT Article 6 and PCT Article 5). As a consequence, the international search, upon which this statement is based, has been incomplete.

The International Search Report revealed ten documents of importance:

D1) EP 0324037 A1 (AROONSAKUL, CHAOVANEE), 19 July 1989 (19.07.89), claim 7

D2) WO 9422469 A1 (OHIO UNIVERSITY), 13 October 1994 (13.10.94), claim 1 and the abstract

D3) WO 9410292 A1 (NEUROSPHERES LTD.), 11 May 1994 (11.05.94), page 14, lines 25-26

D4) WO 8805052 A1 (THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND), 14 July 1988 (14.07.88), page 3, line 19 - line 20; page 6, line 17

D5) GB 2198134 A (SANDOZ LTD.), 8 June 1988 (08.06.88), page 24, line 1 - line 3; page 26, line 1 - line 3; page 26, line 14 - line 17

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V.

D6) WO 9012811 A1 (THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND), 1 November 1990 (01.11.90), page 15, line 16, claims 1, 10

D7) WO 9615226 A1 (NEUROSPHERES HOLDINGS LTD.), 23 May 1996 (23.05.96), page 7, line 17 - page 8, line 2; page 8, line 15 - line 19

D8) WO 9204442 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA), 19 March 1992 (19.03.92)

D9) Dialog Information Services, File 155, Medline, Dialog accession no. 05805167, Medline accession no. 89262444, Morisawa K et al: "Factors contributing to cerebral hypomyelination in the growth hormone-deficient little mouse", Neurochem Res (UNITED STATES) Feb 1989, 14 (2) p 173-7

D10) Progress in Neurobiology, Volume 56, 1998, Christine C. Stichel et al, "Experimental strategies to promote axonal regeneration after traumatic central nervous system injury" page 119 - page 148

D1 discloses a method for alleviating the symptoms of CNS diseases, e.g. Parkinson´s disease. The method comprises i.a. introducing human growth hormone into the blood stream of the patient (see claim 7). The patient is also treated with vasodilater and non-steroidal anti-inflammatory drugs to ensure that the hormone is delivered to the brain (see column 8, lines 43-47).

The wording "damage" of claim 1 is considered to include also damage to the CNS caused by disease, such as Parkinson´s disease.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V.

Thus, since it is previously known from D1 to use growth hormone in the treatment of CNS diseases such as Parkinson´s disease claims 1-2, 4-6 and 8-10 are not considered to be novel in relation to D1 irrespective of the underlying mechanism of action. That is, if a drug is known for treatment of a disease, the mere discovery of the mechanism by which the drug functions to alleviate this disease is not considered to contribute to novelty or inventive step to the second medical indication for the same or related diseases if no unexpected effect can be shown to be present. Moreover, it is considered to be obvious to a person skilled to use a substance that will increase the release of endogenous growth hormone instead of growth hormone itself in the treatment. Therefore, claim 3 is not considered to involve an inventive step.

D2 concerns a method for improving the learning and memory functions of an individual by treatment with somatotropin (growth hormone) or related compounds. Somatotropin is also useful for treating brain injury, mental retardation and degenerative diseases such as Alzheimer´s disease (see claim 1 and the abstract). Therefore, in accordance with the above reasoning for D1, claims 1-6 and 8-10 are not considered to be novel in relation to D2. Moreover, since it is known from D2 to treat brain injuries with growth hormone it is considered obvious to the skilled person to treat brain injuries caused by e.g. trauma. Therefore, claim 7 is not considered to involve an inventive step.

D3 concerns a method for preparing differentiated cells from neural stem cells. The method involves culturing the cells in the presence of i.a. growth hormone.

None of D1-D3 discloses that it is possible to propagate progenitor cells, stem cells and/or cells derived from said cells in vitro in the presence of growth hormone. Therefore, claim 13 is considered to fulfil the requirements of novelty, inventive step and industrial applicability.

D4 pertains to heptapeptide analogs of somatostatin which inhibit secretion of growth hormone. The compounds can be used to therapeutically affect the CNS, e.g. for the treatment of Alzheimer´s disease (see page 6, lines 15-17, 31 and claims 6-7).

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V.

D5 discloses substituted alpha-amino acids. The compounds are used for the treatment of disorders associated with excess growth hormone (i.e. it is considered that the compounds decrease the level of growth hormone) and CNS degenerative disorders (see claim 44).

D6 concerns linear octapeptide analogs of somatostatin which inhibit secretion of growth hormone. The compounds can be used to treat Alzheimer´s disease (see page 15, line 16).

However, none of D4-D6 discloses or suggests the use of a substance that decreases the concentration of growth hormone in the treatment of axonal damage or damage to the spinal cord. Therefore, present claims 11-12 are considered to fulfil the requirements of novelty, inventive step and industrial applicability.

D7 concerns the regulation of neural stem cell proliferation. It is known from D7 that glial scar, which result from gliosis injury of brain or spinal cord, may prevent neuronal axons from re-establishing connections across the injury region, and that proliferation of neural stem cells in response to injury may be a factor in the development of gliosis. Therefore, D7 provides a method of regulating the proliferation of neural stem cells, which method involves a regulatory factor selected from, for instance, heparan sulfate, CNTF, retionic acid, activin, interleukins, and EGF (see the claims).

D8 discloses glial antiproliferative proteins which are useful in promoting regeneration of nervous tissue following trauma of injury or surgery.

However, none of D7 or D8 discloses or suggests the use of substance that upon administration will lead to a decreased concentration of growth hormone. Therefore, present claims 11-12 are considered to be non-obvious in relation to D7 and D8.

In D9 it has been suggested that hypomyelination might result from reduced oligodendroglial proliferation due to growth hormone deficiency.

D10 concerns experimental strategies to promote axonal regeneration after traumatic central nervous system injury.

.../...

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V.

D9 and D10 are considered to show the general state of the art.

CLAIMS

1. Use of a substance that upon administration to a patient will lead to an increased concentration of growth hormone or a functionally equivalent analogue thereof for the production of a medicinal product for treatment of an abnormal condition affecting neural stem cells, progenitor cells and/or cells derived from stem cells or progenitor cells.

2. Use according to claim 1, wherein said substance is growth hormone or a functionally equivalent analogue thereof.

3. Use according to claim 1, wherein said substance upon administration will increase the release of endogenous growth hormone.

4. Use according to any one of the claims 1-3, wherein said condition affects the oligodendroglia, astroglia, and/or neuronal cells.

5. Use according to any one of the claims 1-4, wherein said condition affects non-cholinergic neuronal cells, cholinergic neuronal cells, or glial cells.

6. Use according to any one of the claims 1-5, wherein said condition is a CNS damage or deficit.

7. Use according to any one of the claims 1-6, wherein said condition is neural cell loss.

8. Use according to any one of the claims 1-7, wherein said condition is memory loss.

9. Use according to any one of the claims 1-8, wherein said condition is caused multiple sclerosis, hypoxic injury, ischemic injury, traumatic injury, Parkinson's disease, and/or demyelinating disorder.

10. Use according to any one of the claims 1-9, wherein said medicinal product is formulated for intravenous infusion, intramuscular injection or subcutaneous injection.

11. Use according to any one of the claims 1-10, wherein said medicinal product is formulated so that the

active substance will pass into the ventricles of the patient's brain when it is administered to a patient.

12. Use according to any one of the claims 1-11, wherein said medicinal product is formulated so that the active substance will pass into the cerebrospinal fluid of the patient when it is administered to a patient.

13. Use of a substance that upon administration to a patient will lead to a decreased concentration of growth hormone or a functionally equivalent analogue thereof for the production of a medicinal product for treatment of an abnormal condition affecting the central nervous system.

14. Use according to claim 13, wherein said substance is a negatively regulating growth hormone binding protein, a functionally equivalent analogous thereof, an antibody against growth hormone, a biologically active growth hormone receptor inhibitor, and/or an inhibitor of endogenous growth hormone release.

15. Use according to claim 13 or 14, wherein said abnormal condition is the consequence of axonal damage caused by concussion, axonal damage caused by head trauma, axonal damage caused by small vessel disease in the CNS, damage to the spinal cord after disease and/or trauma.

16. A method of inducing lineage determination, propagating and/or inducing or maintaining the genesis of neurons, oligodendrocytes, astroglial cells from progenitor cells, stem cells and/or cells derived from said cells by administration of an effective amount of growth hormone or a functionally equivalent analogue thereof to stem cells, progenitor cells, neurons astroglial cells and/or oligodendrocytes in vitro.

17. A method of inducing lineage determination or inducing or maintaining the genesis of neurons, oligodendrocytes, astroglial cells from progenitor cells or stem cells in, or derived from, the central or periferal nervous system in a patient, wherein a pharmaceutically effective amount of a substance that will lead to an in-

creased concentration of growth hormone or a functionally equivalent analogue thereof is administered to said patient.

18. A method according to claim 17, wherein said substance is growth hormone or a functionally equivalent analogue thereof.

19. A method according to claim 17, wherein said substance is a substance that increases the release of endogenous growth hormone.

20. A method according to claim 17, for treatment of an abnormal condition affecting the nervous system of a patient.

21. A method according to claim 20, wherein said condition affects the oligodendroglia, astroglia, and/or neuronal cells.

22. A method according to claim 22, wherein said condition affects the non-cholinergic neuronal cells, cholinergic neuronal cells, or glial cells.

23. A method according to claim 20, wherein said condition is a CNS damage or deficit.

24. A method according to claim 23, wherein said condition is neural cell loss.

25. A method according to claim 23, wherein said condition is memory loss.

26. A method according to claim 23, wherein said condition is caused by at least one factor selected from the group consisting of multiple sclerosis, hypoxic injury, ischemic injury, traumatic injury, Parkinson's disease, and demyelinating disorder.

27. A method according to claim 17, wherein said substance is administered by intravenous infusion, intramuscular injection or subcutaneous injection.

28. A method according to claim 17, wherein brain cells are removed from the patient after said administration, said brain cells then being propagated in vitro, followed by transplantation of the obtained cells back into the brains of the patient.

29. A method according to claim 28, wherein an effective amount of growth hormone or a functionally equivalent analogue thereof is administered to said brain cells during in vitro propagation.

30. A method of reducing the genesis of oligodendrocytes, neurons, astroglial cells from progenitor cells or stem cells in, or derived from, the central or periferal nervous system in a patient, wherein a pharmaceutically effective amount of a substance that will lead to a decreased concentration of growth hormone or a functionally equivalent analogue thereof is administered to said patient.

31. A method according to claim 30, wherein said substance is administration to the periferal or central nervous system of said patient.

32. A method according to claim 30, wherein said substance is selected from the group consisting of negatively regulating growth hormone binding proteins, functionally equivalent analogous thereof, antibodies against growth hormone, biologically active growth hormone receptor inhibitors, and inhibitors of endogenous GH release.

33. A method according to claim 30, for treatment of a central nervous system injury.

34. A method according to claim 33, wherein said injury is the consequences of a factor selected from the group consisting of axonal damage caused by concussion, axonal damage caused by head trauma, axonal damage caused by small vessel disease in the CNS, damage to the spinal cord after disease or trauma.